PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	12.11.2004
Applicant's or agent's file reference: ABL-013-PCT2	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE 03/00193	07.11.2003	08.11.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/18

Applicant
ABLYNX N.V. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also: For an additional opportunity to submit amendments, see Rule 66.4.
   For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
   For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 08.03.2005

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-56, 58-65, 67-77	as originally filed
57, 66	received on 10.03.2004 with letter of 10.03.2004

Claims, Numbers

1-66	as originally filed

Drawings, Sheets

1/9, 2/9, 4/9-9/9	as originally filed
3/9	received on 10.03.2004 with letter of 10.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10,20,29,38,48

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10,20,29,38,48

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-9,11-19,21-28,30-37,39-47,49-65
Inventive step (IS)	Claims	1-9,11-19,21-28,30-37,39-47,49-66
Industrial applicability (IA)	Claims	1-66?

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

Sequence listings filed, 41 pages, with the letter of 10.03.04, are filed after the filing date of the application and do not form part of the description and will not be annexed to this communication/report (Rule 13ter (f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15,25,34,43 and 56 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67 (iv) PCT. Consequently no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

No international search report was established for the subject-matter of claims 10,20,29,38 and 48, see sheet 210 of the ISR. Therefore no opinion with respect to novelty, inventive step and industrial applicability will be formulated (Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
   D1: EP-A-0 952 218
   D2: WO 99/23221 A
   D3: ELS CONRATH K ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 10, 9 March 2000, pages 7346-7350,
   D4: TANHA J ET AL: JOURNAL OF IMMUNOLOGICAL METHODS, vol. 263, no. 1-2, 1 May 2002 (2002-05-01), pages 97-109

2. The subject-matter of claim 1 is not novel (Article 33(2) PCT).
   D1 describes bispecific antibodies which falls within the wording of present claim 1, see e.g. claim 20 of D1.
   The same holds true for the subject-matter of claim 66.

3. D2 and D3 describes multivalent single polypeptide antibodies of camel, see e.g. claims of D2. D3 further discusses, by describing the same principal of designing

bivalent antibodies construct (VHH, beta-lactamase, lysozyme) as in the present application, the plasma stability of the described bifunctional construct, see e.g. p.7350, 1. col., 2.par. ff. and p.7350 last par.

No special technical effect of the claimed subject-matter of claims 2-9,11-19,21-28,30-37,39-47,49-65 could be identified in the present application with respect to the cited prior art (D1-D3) which would allow an acknowledgment of an inventive step according to Article 33(3) PCT.
Furthermore no experimental data nor comparative examples for the claimed antibody molecules are provided in the present application which clearly underline the claimed effect of a more stable antibody with a prolonged half-time, see p.14, l.13 ff. . e.g. the IC50 values are always higher for the bispecific VHH as for the monovalent construct, see p.74, Table 11.

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII
Certain observations on the international application

The dependency of claims 14,15,24,25,42,56 is not clear. Furthermore the claims refers to two different categories (product and use). Article 6 PCT is thus not fulfilled for these claims.